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EXAMINER	
LEFFERS JR, GERALD G	

ART UNIT	PAPER NUMBER
1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/800,520	IBA ET AL.	
	Examiner	Art Unit	
	Gerald G Leffers Jr., PhD	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34,41-46 and 53-57* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34,41-46 and 53-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application on 8/18/2004 after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicants' submission filed on 7/27/2004 has been entered.

Response to Amendment

In the response filed 7/27/2004 several claims were amended (claims 34, 44-46) and several claims were cancelled (claims 35-40, 47-52). Claims 34, 41-46 & 53-57 are pending in the instant application and are under consideration. Any rejection of record not addressed in the instant action is withdrawn. This action is not final.

A new grounds of rejection is included herein that has not been made previously. Over the course of prosecution for the instant application the nature of the invention has changed to such a degree that the claimed invention can no longer be grouped as part of the invention elected by original presentation (i.e. Group II, original claims 8-9; see page 4 of applicants' preliminary amendment filed 3/8/2001). The originally elected invention was directed to a short-lived transcript drug resistance gene characterized by having a base sequence of a short-lived neomycin resistance gene, puromycin resistance gene or hygromycin resistance gene. As currently worded, the pending claims read on expression vectors used to generate prepackaging cells for eukaryotic viral vectors and, as such, are grouped along with the invention prosecuted in

the parent application, U.S. Application Serial No. 09/214,465 (now U.S. Patent No. 6,743,620). For this reason, it is now proper to analyze the pending claims with regard to Obviousness Double Patenting over the issued claims of the parent application. An Obviousness-Type Double Patenting rejection over the issued claims is presented below.

Priority

It is requested that applicants amend the first sentence of the specification to update the status of the parent application to which the instant application claims priority (i.e. 09/214,465 has issued as U.S. Patent No. 6,743,620), and to indicate that the parent application was the National Stage application for international application PCT/JP/04592 (filed 12/12/1997).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 34, 41-46 & 53-57 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This rejection is maintained for reasons of record in the office action mailed 5/19/2004, and which are repeated below.**

Claims 34, 41-46 & 53-57 are directed to a broad class of vectors and methods of use thereof to express desired genes in a given cell. Claims 34, 41-45 have been amended to limit the scope to expression vectors comprising (i) a gene encoding a viral structural protein, (ii) a gene encoding a selectable drug-resistance gene having an mRNA-destabilizing sequence under control of a promoter, and (iii) where the promoter transcribes the gene encoding a viral structural protein when in a prepackaging cell. Claims 46 & 53-55 have been amended to read in the preamble as being directed to "[an] expression vector for a gene encoding a viral structural gene", but do not actually recite that the gene encoding the viral structural gene is present in the vector. Thus, the only structural/functional element that is explicitly recited in claims 46 & 53-55 is the presence of a selectable drug resistance gene having an mRNA-destabilizing sequence that produces a short-lived transcript of the drug-resistance gene. Claims 56-57 do recite that cells comprising the vector of claim 46 express a gene encoding a viral structural protein. At least two of the claims (claims 45 & 57) are directed to use of the vectors in gag/pol expressing cells.

Despite the amendment of the claims to attempt to limit the scope of vectors and methods to ones where the vector expresses a viral structural protein, the rejected claims continue to encompass embodiments for which there is no support in the originally filed specification and claims. There is no recitation in any of the rejected claims concerning the presence of recombinase recognition sequences on either side of the selectable drug-resistance gene having an mRNA-destabilizing sequence (e.g. for vectors corresponding to vector A or B of the instant specification), LTR sequences for those vectors corresponding to vector B of the instant specification), and polyA sequences for either type of construct. This allows the rejected claims

to read on embodiments never contemplated in the originally filed application (e.g. a vector meeting the limitations of claim 34 where the vector lacks recombinase recognition sequences flanking the selectable drug resistance gene but which does comprise an IRES sequence separating the selectable drug resistance gene and the sequence encoding a viral structural protein). In the specification, the short-lived transcript drug resistance genes are only described in the context of selecting cells comprising very specific expression constructs (e.g. constructs A & B, pages 8-12; see especially page 14, line 16 through page 15, line 23) integrated into the host cell genome for the purpose of preparing pre-packaging cells useful for the preparation of retroviral gene transfer vectors (e.g. pages 16-17, bridging paragraph; page 22, 1st paragraph). No broader use for the recited short-lived transcript drug resistance genes is contemplated in the originally filed specification or claims. Thus, the broader scope of use encompassed by the rejected claims is impermissible NEW MATTER.

In response to similar grounds of rejection in the previous office actions, applicants have attempted to point to specific passages of the instant specification for support for the broadly claimed vectors and methods. Each of the passages cited in applicants' response was solely directed to the use of the short-lived transcript drug-resistance gene in the context of the prepackaging cells of the invention (e.g. construct A used to express a viral structural gene such as VSV-G). For example, in the first passage cited by the response filed 2/24/2004, the inventors teach "[The present inventors] have also utilized the phenomenon that, in the preparation of the above-mentioned prepackaging cells, cells requiring the expression of a stronger resistance marker can be efficiently screened by using a drug resistance marker gene one the function of which has been deteriorated..." (examiner's emphasis added). The second passage cited by

applicants is present at the bridging paragraph for pages 16-17 of the instant specification. Read in the context of the paragraph preceding the cited passage, it is clear that the phrase "As the drug resistance gene..." at the beginning of the cited passage directs the teachings of the passage to the use of the modified drug-resistance gene in the context of preparing the prepackaging cells of the invention. The teachings with regard to the nature of the modified drug resistance gene are clearly only intended for use in the prepackaging constructs of the invention and are not taught for use in a broader context. Finally, the experiment described with regard to selection of cells expressing high levels of VSV-G utilize a vector meeting the limitations of construct A as described in the specification (e.g. page 14, last paragraph). For example, a construct comprising, in order, a promoter, recombinase recognition sequence, a drug resistance gene, a polyA addition signal, the recombinase recognition sequence, the viral structural gene (e.g. a gene encoding VSV-G for pseudotyping of retroviral virions) and a polyA addition signal. The passage cited by applicants clearly indicates the expression of the viral structural gene encoding VSV-G only after addition of the Cre recombinase to excise the fragment encoding the modified drug-resistance gene. Thus, the third passage cited in the response is directed explicitly to a vector meeting the limitations of construct A of the invention and is not representative of a broader teaching of vectors other than construct A or construct B for expressing a foreign gene.

As yet applicants have not been able to point to a specific portion of the originally filed claims that provides support for vectors and methods that are broader in scope than those featuring the use of vectors meeting the structural/functional characteristics of vector A and vector B as taught in the instant specification. At most, the instant specification provides support for the use of vectors reciting each of the characteristics for either vector A or vector B as

defined in the instant specification (e.g. see especially page 14, line 16 through page 15, line 23; page 10, lines 17-25). It would be remedial with regard to the instant rejection to amend the claims to include the structural limitations recited on page 14-line 16 to page 15-line 23 for DNA construct A or DNA construct B.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 56-57 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **These are new rejections that are necessitated by applicants' amendment of the claims in the response filed 7/27/2004.**

The rejected claims are vague and indefinite in that there is no clear and positive prior antecedent basis for the phrase "the gene encoding a viral structural protein". Claim 46, upon which both rejected claims are dependent, does not actually recite that the gene encoding a viral structural protein is present on the expression vector.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The rejected claims are drawn towards expression vectors comprising a drug resistance gene as a selection marker that comprises an mRNA destabilizing sequence and which is intended for expression of a gene encoding a viral structural protein in a prepackaging cell (e.g. claim 46). The mRNA destabilizing sequence can be obtained from the untranslated region of a gene encoding c-fos (e.g. claim 53). Cells comprising the expression vector are claimed (claim 55). The selectable marker gene can encode neomycin resistance, puromycin resistance or hygromycin resistance (claim 54). The following rejections are necessitated by the fact that the rejected claims do not comprise a limitation that the gene encoding a viral structural gene is actually present in the expression vector.

Claims 46 & 53-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pavlakis et al (U.S. Patent No. 5,972,596; see the entire patent) in view of DePonti-Zilli et al (PNAS USA 1988, Vol. 85, pages 1389-1393; see the entire reference). **This is a new rejection necessitated by applicants' amendment of the claims on 7/27/2004.**

The Pavlakis patent (the '596 patent) teaches methods for identifying and correcting inhibitory/instability sequences (INS) within the coding region of an mRNA of a desired protein such that the level of production of the desired protein can be increased (e.g. Abstract; columns 5-6, bridging paragraph). Pavlakis et al teach that in order to evaluate whether putative regulatory sequences are sufficient to confer mRNA stability control (e.g. destabilization) on an mRNA transcript, DNA sequences coding for the suspected INS region are fused to an indicator (or reporter) gene to create a gene coding for a hybrid mRNA. The DNA sequence fused to the indicator gene can be cDNA, genomic DNA or synthesized DNA. Examples of acceptable reporter genes known in the art are genes encoding neomycin resistance protein (note: neomycin itself is not a protein), B-galactosidase, chloramphenicol resistance, luciferase, B-globin, PGK1 and ACT1.

The '596 patent teaches that the stability and/or utilization of the mRNAs generated by fusion of the indicator genes and sequences suspected of encoding an INS region is tested by transfecting the hybrid genes into host cells which are appropriate for the expression vector used to clone and express the mRNAs. The resulting levels of mRNA are determined by standard methods of determining mRNA stability (e.g. Northern blots, S1 nuclease mapping or PCR methods), and the resulting levels of protein produced are quantitated by protein measuring assays (e.g. ELISA, western blot, etc.). The INS regions are identified by a decrease in the protein expression and/or stability of the hybrid mRNA as compared to the control indicator RNA (e.g. column 13, lines 44-62). Once INS regions of a particular target gene are identified, the coding sequence can be altered such that the expressed polypeptide is the same one encoded by the original coding sequence, or a conservative variant of the original polypeptide (e.g.

column 16, section 3). Mutated or altered coding sequences designed to remove INS sequences are then tested in the same manner as was used to identify the INS sequence (e.g. column 16, lines 45-56).

The Pavlakis et al patent teaches that genes encoding or suspected of encoding mRNAs containing inhibitory/instability regions within the coding region are particularly relevant to the invention (column 12, lines 34-36). In particular, c-fos is identified as a protein whose coding sequence is known in the art to comprise INS sequences that result in the c-fos transcript being unstable such that it is rapidly degraded (e.g. column 2, lines 8-13; column 12, lines 15-35). Example 3 is directed towards an embodiment wherein fragments encoding c-fos are operatively linked to a sequence encoding a reporter protein (i.e. RSV gag).

The Pavlakis et al patent does not exemplify an embodiment where the neomycin resistance gene is operatively linked to a coding sequence comprising an INS, although it does suggest that the neomycin resistance gene would be an effective reporter in their system. The '596 patent doesn't explicitly teach the fusion of a coding sequence for neomycin resistance to any part of the c-fos gene.

The DePonti-Zilli et al reference teaches the characterization of a 40 base-pair sequence in the 3' end of the B-actin gene with regard to regulating B-actin mRNA transcription during myogenesis (e.g. Abstract). DePonti-Zilli et al teach that fusion of the 40 base-pair sequence 3' to the genes for a-cardiac-actin and neomycin-resistance protein confers the B-actin mRNA regulatory pattern on the hybrid constructs when introduced into C2C12 cells (e.g. Abstract; Figure 3). Hybrid transcript levels were detected by S1 nuclease protection assays using end-labeled neomycin resistance gene probes (e.g. page 1389, column 2, "RNA Isolation and

Nuclease S1 Analysis"; Figure 3). The authors conclude that although the 40 base-pair sequence from B-actin fused to the neomycin resistance coding sequence conferred B-actin transcriptional regulatory patterns on the hybrid transcript, the control was not at the level of RNA stability (e.g. pages 1392-1393, bridging paragraph). Therefore, DePonti-Zilli et al do not teach the construction and use of a short-lived transcript drug resistance gene.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the neomycin resistance gene in the methods of Pavlakis et al as an indicator to identify instability sequences (INS) of a gene encoding a transcript known or suspected to possess such INS sequences because Pavlakis et al teach it is within the skill of the art to use the gene encoding neomycin resistance as a reporter gene to identify such instability sequences and because DePonti-Zilli et al teach the use of the neomycin resistance gene to characterize a putative transcriptional regulatory sequence when the putative regulatory sequence is fused to the sequence encoding neomycin resistance. One would have been motivated to do so in order to receive the expected benefit, as suggested by Pavlakis et al and actually exemplified by DePonti-Zilli et al, of being able to characterize the ability of a putative transcriptional regulatory sequence to affect the stability/utilization of a neomycin resistance gene transcript. Absent any evidence to the contrary, there would have been a reasonable expectation of success in utilizing the neomycin resistance gene as a marker to identify transcriptional regulatory sequences that destabilize the neomycin resistance transcript. In cases in which such a destabilizing element is identified using the neomycin resistance gene as a reporter, one would necessarily have generated a short-lived transcript drug resistance gene.

The limitation of a cell transformed with the vector of claim 46 and selected with the corresponding drug does not necessarily confer any structural/functional distinction on the cell that would not be present in the cells taught by Schuler. Differences in gene expression for the constructs taught in the specification appear to be due to the location of insertion of the targeting vector in the specification and not due to some structural aspect of the claimed vector itself.

Claims 46 & 53-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pavlakis et al (U.S. Patent No. 5,972,596; see the entire patent) in view of Gritz et al (Gene 1983, Vol. 25, pages179-188). **This is a new rejection necessitated by applicants' amendment of the claims on 7/27/2004.**

The teachings of the Pavlakis et al patent (the '596 patent) are described above and applied as before, except: the Pavlakis et al patent does not explicitly teach an embodiment where the hygromycin resistance gene is operatively linked to a coding sequence comprising an INS.

Gritz et al teach the cloning and characterization of the plasmid-borne gene (hph) encoding hygromycin B phosphotransferase from E. coli (e.g. Abstract). Gritz et al teach that when placed in the appropriate shuttle vector, hph allows for direct selection of cells comprising the shuttle vector in yeast as well as for E. coli (e.g. Abstract). This selection varies for different concentrations of hygromycin B and different constructs comprising different transcription initiation points (e.g. Figure 5 & Table II). Thus, Gritz et al teach that different levels of hygromycin B phosphotransferase in a cell expressing the hph gene can be detected by genetic selection. In addition to detecting the levels of hygromycin B phosphotransferase by direct

genetic selection, Gritz et al teach a method for directly assaying enzyme activity in a cell extract (e.g. page 181, column 1, last paragraph; Table 1).

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the hygromycin resistance gene in the methods of Pavlakis et al as an indicator to identify instability sequences (INS) of a gene encoding a transcript known or suspected to possess such INS sequences because Pavlakis et al teach it is within the skill of the art to use a gene encoding an mRNA which is expressed at relatively high levels (defined as being stable enough or highly expressed enough such that any decrease in the level of the mRNA or expressed protein can be detected by standard methods) as a reporter gene to identify such instability sequences and because Gritz et al teach that the gene encoding hygromycin B phosphotransferase is sufficiently well expressed that one can assay for its presence by direct genetic selection or by enzymatic assay in either prokaryotic or eukaryotic systems. One would have been motivated to do so in order to receive the expected benefit of being able to easily assay for protein encoded by the hybrid transcripts comprising the putative INS sequence, as taught by Pavlakis et al, by either enzymatic means or by direct genetic selection, as taught by Gritz et al. Absent any evidence to the contrary, there would have been a reasonable expectation of success in practicing the methods taught by Pavlakis et al with the hph gene, as taught by Gritz et al, to identify putative destabilizing INS regions in a desired gene transcript. In cases in which such a destabilizing element is identified using the hygromycin resistance gene as a reporter, one would necessarily have generated a short-lived transcript drug resistance gene.

The limitation of a cell transformed with the vector of claim 46 and selected with the corresponding drug does not necessarily confer any structural/functional distinction on the cell

that would not be present in the cells taught by Schuler. Differences in gene expression for the constructs taught in the specification appear to be due to the location of insertion of the targeting vector in the specification and not due to some structural aspect of the claimed vector itself.

Claims 46 & 53-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pavlakis et al (U.S. Patent No. 5,972,596; see the entire patent) in view of de la Luna et al (Gene 1988, Vol. 62, pages 121-126). **This is a new rejection necessitated by applicants' amendment of the claims on 7/27/2004.**

The teachings of the Pavlakis et al patent (the '596 patent) are described above and applied as before, except:

The Pavlakis et al patent does not explicitly teach an embodiment where the puromycin resistance gene is operatively linked to a coding sequence comprising an INS. The '596 patent doesn't explicitly teach the fusion of a coding sequence for puromycin resistance to any part of the c-fos gene.

The de la Luna et al reference teaches the construction and characterization of different vectors expressing the puromycin-resistance protein (puromycin-N-acetyl-transferase or PAC) for the efficient transformation of mammalian cells (e.g. Abstract). The de la Luna et al reference teaches that one can detect varying levels of PAC expressed from different constructs in COS-1 cells based upon an enzymatic assay (e.g. Table 1). The reference further teaches that one can detect different levels of PAC expression from the different expression constructs by genetic selection for stably transformed cells (e.g. Table II, expressed as the number of stable transformants per 10^6 recipient cells).

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the puromycin resistance gene in the methods of Pavlakis et al as an indicator to identify instability sequences (INS) of a gene encoding a transcript known or suspected to possess such INS sequences because Pavlakis et al teach it is within the skill of the art to use a gene encoding an mRNA which is expressed at relatively high levels (defined as being stable enough or highly expressed enough such that any decrease in the level of the mRNA or expressed protein can be detected by standard methods) as a reporter gene to identify such instability sequences and because de la Luna et al teach that the gene encoding puromycin resistance is sufficiently well expressed that one can assay for its presence by genetic selection or by enzymatic assay. One would have been motivated to do so in order to receive the expected benefit of being able to easily assay for protein encoded by the hybrid transcripts comprising the putative INS sequence, as taught by Pavlakis et al, by either enzymatic means or by genetic selection, as taught by de la Luna et al. Absent any evidence to the contrary, there would have been a reasonable expectation of success in practicing the methods taught by Pavlakis et al with the puromycin resistance gene, as taught by de la Luna et al, to identify putative destabilizing INS regions in a desired gene transcript. In cases in which such a destabilizing element is identified using the puromycin resistance gene as a reporter, one would necessarily have generated a short-lived transcript drug resistance gene.

The limitation of a cell transformed with the vector of claim 46 and selected with the corresponding drug does not necessarily confer any structural/functional distinction on the cell that would not be present in the cells taught by Schuler. Differences in gene expression for the

constructs taught in the specification appear to be due to the location of insertion of the targeting vector in the specification and not due to some structural aspect of the claimed vector itself.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 46 & 53-55 are rejected under 35 U.S.C. 102(b) as being anticipated by Schuler et al (Cell, December 1988, Vol. 55, pages 1115-1122). **This is a new rejection necessitated by applicants' amendment of the claims on 7/27/2004.**

Schuler teach an experiment wherein coding sequences for neomycin resistance (neo) were operatively linked to untranslated regions obtained from genes encoding GM-CSF, c-fos, and c-myc. Shuler et al teach that the transcripts from these fusions had a shorter half-life following expression than the neomycin resistance transcript alone (e.g. Figure 4). The vectors taught by Schuler et al for expression of these genes are necessarily "expression" vectors. One of skill in the art would expect that the fusion transcripts described by Schuler et al would provide at least some degree of drug resistance as they encode the entire neomycin gene. The skilled artisan would also expect that one would be able to select cells in which expression is increase due to the presence of the destabilization sequences in the fusion transcripts because the fusion transcripts of Schuler et al do not appear to be structurally any different from those taught in the instant application.

The limitation of a cell transformed with the vector of claim 46 and selected with the corresponding drug does not necessarily confer any structural/functional distinction on the cell that would not be present in the cells taught by Schuler. Differences in gene expression for the constructs taught in the specification appear to be due to the location of insertion of the targeting vector in the specification and not due to some structural aspect of the claimed vector itself.

Because the Office does not have the facilities for examining and comparing the applicant's product with the products of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed products and the products of the prior art (e.g. that the products of the prior art do not possess the same material structural and functional characteristics of the claimed product). See in re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 34, 41-46, 53-57 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 6-7, 13, 16, 20 & 22-23 of U.S.

Patent No. 6,743,620 B1. Although the conflicting claims are not identical, they are not patentably distinct from each other because of the following reasons. **This is a new rejection.**

Claims 34, 41-46 & 53-57 of the instant application are directed to a broad class of vectors and methods of use thereof to express desired genes in a given cell. Claims 34, 41-45 have been amended to limit the scope to expression vectors comprising (i) a gene encoding a viral structural protein, (ii) a gene encoding a selectable drug-resistance gene having an mRNA-destabilizing sequence under control of a promoter, and (iii) where the promoter transcribes the gene encoding a viral structural protein when in a prepackaging cell. Claims 46 & 53-55 have been amended to read in the preamble as being directed to "[an] expression vector for a gene encoding a viral structural gene", but do not actually recite that the gene encoding the viral structural gene is present in the vector. Thus, the only structural/functional element that is explicitly recited in claims 46 & 53-55 is the presence of a selectable drug resistance gene having an mRNA-destabilizing sequence that produces a short-lived transcript of the drug-resistance gene. Claims 56-57 do recite that cells comprising the vector of claim 46 express a gene encoding a viral structural protein. At least two of the claims (claims 45 & 57) are directed to use of the vectors in gag/pol expressing cells.

The claims of the '620 patent are directed to specific embodiments that meet all of the structural/functional limitations of the instant claims. Claim 1 is directed to a DNA construct for regulating expression of a sequence encoding a viral structural protein that is cytotoxic, comprising a promoter, a recombinase recognition sequence, a drug resistance gene, a polyA addition signal, a recombinase recognition sequence, the viral structural protein gene and a polyA addition signal, arranged in this order. The drug resistance gene can encode a short-lived

transcript that results in neomycin drug resistance, puromycin drug resistance or hygromycin drug resistance (e.g. claims 6-7). The DNA construct can be inserted into prepackaging cells expressing retroviral gagpol and used to produce retroviral particals comprising the viral structural gene product (e.g. claims 13, 16, 20 and 22-23). Thus, the cited claims of the '620 patent are specific embodiments of, and are totally encompassed by, the rejected claims. Therefore, the cited claims of the '620 patent anticipate, and necessarily make obvious, the rejected claims of the instant application.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald G Leffers Jr., PhD whose telephone number is (571) 272-0772. The examiner can normally be reached on 9:30am-6:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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